

CLAIMS

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1. An isolated nucleic acid sequence containing at least one unmethylated CpG dinucleotide and having a formula:



10 wherein at least one nucleotide separates consecutive CpGs;  $X_1$  is adenine, guanine, or thymine;  $X_2$  is cytosine or thymine; N is any nucleotide and  $N_1 + N_2$  is from about 0-  
26 bases with the proviso that  $N_1 + N_2$  does not contain a CCGG quadmer or more than one CCG or CGG trimer; and the nucleic acid sequence is from about 8-30 bases in  
15 length.

2. The nucleic acid sequence of claim 1, wherein  $X_1$  is thymine
3. The nucleic acid sequence of claim 1, wherein  $X_2$  is thymine.
- 20 4. The nucleic acid sequence of claim 1, which is GTCG (T/C) T or TGACGTT.
5. The nucleic acid sequence of claim 1, wherein the sequence is TGTCG (T/C) T.
- 25 6. The nucleic acid sequence of claim 1, which is TCCATGTCGTTCTGTCGTT.
7. The nucleic acid sequence of claim 1, which is TCCTGACGTTCTGACGTT.
8. The nucleic acid sequence of claim 1, which is TCGTCGTTTTGTCGTTTTGTCGTT.
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9. An isolated nucleic acid sequence containing at least one unmethylated CpG dinucleotide and having the formula:



5 wherein at least one nucleotide separates consecutive CpGs;  $X_1X_2$  is selected from the group consisting of GpT, GpG, GpA, ApT and ApA;  $X_3X_4$  is selected from the group consisting of TpT or CpT; N is any nucleotide and  $N_1N_2$  is from about 0-26 bases with the proviso that  $N_1$  and  $N_2$  does not contain a CCGG quadmer or more than one CCG or CGG trimer; and the nucleic acid sequence is from about 8-30 bases in length.

10 10. The nucleic acid sequence of claim 9, wherein the nucleotide that separates at least two consecutive CpGs is thymine.

11. The nucleic acid sequence of claim 9, wherein  $X_3$  and  $X_4$  are thymine.

15 12. A nucleic acid sequence of any of claims 1 or 9, wherein at least one nucleotide has a phosphate backbone modification.

13. The nucleic acid sequence of claim 12, wherein the phosphate backbone modification  
20 is a phosphorothioate or phosphorodithioate modification.

14. The nucleic acid sequence of claim 13, wherein the phosphate backbone modification occurs at the 5' end of the nucleic acid.

25 15. The nucleic acid sequence of claim 14, wherein the modification occurs at the first two internucleotide linkages of the 5' end of the nucleic acid.

16. The nucleic acid sequence of claim 13, wherein the phosphate backbone modification occurs at the 3' end of the nucleic acid.

30 17. The nucleic acid sequence of claim 16, wherein the modification occurs at the last five internucleotide linkages of the 3' end of the nucleic acid.

18. A method of stimulating immune activation in a subject, wherein the stimulation is predominantly a Th1 pattern of immune activation, comprising administering to the subject a nucleic acid sequence having the formula of claim 1 or claim 9.

5 19. The method of claim 18, wherein the subject is human.

20. A method of stimulating cytokine production in a subject comprising administering to the subject a nucleic acid sequence having the formula of claim 1 or claim 9.

10 21. The method of claim 20, wherein the cytokine is selected from the group consisting of:  
IL-6, IL-12, IFN- $\gamma$ , TNF- $\alpha$  and GM-CSF.

22. The method of claim 20, wherein the subject is human.

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23. The method of claim 20, where the nucleic acid sequence is selected from the group consisting of:

TCCATGTCGCTCCTGATGCT,  
TCCATAACGTTCCCTGATGCT,  
20 TCCATGACGATCCTGATGCT,  
TCCATGGCGGTCCTGATGCT,  
TCCATGTCGGTCCTGATGCT,  
TCCATAACGTCCCTGATGCT,  
TCCATGTCGTTCCCTGATGCT; and  
25 TCGTCGTTTTGTCGTTTTGTCGTT.

24. A method of stimulating NK lytic activity in a subject comprising administering to the subject a nucleic acid sequence having the formula of claim 1 or claim 9.

30 25. The method of claim 24, where the subject is human.

26. The method of claim 24, where the nucleic acid sequence is selected from the group

consisting of:

TCGTCGTTGTCGTTGTCGTT,  
TCCATGACGGTCCTGATGCT,  
TCCATGACGATCCTGATGCT,  
5 TCCATGACGCTCCTGATGCT,  
TCCATGACGTTCCCTGATGCT,  
TCCATAACGTTCCCTGATGCT,  
TCCATCACGTGCCTGATGCT,  
GGGGTCAACGTTGAGGGGGG,  
10 TCGTCGTTTTGTCGTTTTGTCGTT,  
TCGTCGTTGTCGTTTTGTCGTT,  
GCGTGCGTTGTCGTTGTCGTT,  
TGTCGTTTGTCGTTTGTCGTT,  
TGTCGTTGTCGTTGTCGTT; and  
15 TCGTCGTCGTCGTT.

27. A method of stimulating B cell proliferation in a subject, comprising administering to the subject a nucleic acid sequence having the formula of claim 1 or claim 9.

20 28. The method of claim 27, where the subject is human.

25 29. The method of claim 27, where the nucleic acid sequence is selected from the group consisting of:

TCCTGTCGTTCCCTGTCGTT),  
TCCTGTCGTTTTTTGTCGTT,  
TCGTCGCTGTCTGCCCTTCTT,  
TCGTCGCTGTTGTCGTTTCTT,  
30 TCGTCGTTTTGTCGTTTTGTCGTT,  
TCGTCGTTGTCGTTTTGTCGTT; and  
TGTCGTTGTCGTTGTCGTT.

30. A method of stimulating immune activation in a subject comprising administering to a subject an nucleic acid sequence having the formula of claim 1, wherein the nucleic acid sequence acts as an adjuvant.

5 31. The method of claim 30, where the subject is a mammal.

32. The method of claim 30, where the nucleic acid sequence is selected from the group consisting of:

TCCATGACGTTCCCTGACGTT,

10 GTCG (T/C) T; and

TGTCG (T/C) T.

33. A method for treating a subject having an asthmatic disorder by administering to the subject an nucleic acid sequence in a pharmaceutically acceptable carrier having the formula of claim 1.

34. The method of claim 33, where the subject is human.

35. The method of claim 33, where the nucleic acid sequence is  
20 TCCATGACGTTCCCTGACGTT.

36. A method for treating a subject having an autoimmune or other CpG associated disorder by inhibiting CpG-mediated leukocyte activation comprising administering to the subject an inhibitor of endosomal acidification in a pharmaceutically acceptable carrier.

25 37. The method of claim 36, where the subject is human.

38. The method of claim 36, where the inhibitor is selected from the group consisting of: bafilomycin A, chloroquine, and monensin.

30 39. The method of claim 38, where the inhibitor is administered at a dosage of the less than about 10  $\mu$ M.

40. The method of claim 36, wherein the disorder is selected from the group consisting of systemic lupus erythematosus, sepsis, inflammatory bowel disease, psoriasis, gingivitis, arthritis, Crohn's disease, Grave's disease and asthma.

5 41. The method of claim 40, where the disorder is systemic lupus erythematosus.

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